Sofosbuvir: A New Oral Once-Daily Agent for The Treatment of Hepatitis C Virus Infection

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INTRODUCTION

Hepatitis C virus (HCV) is a significant public health problem and the leading cause of liver transplantation and hepatocellular carcinoma.[1] Globally, approximately 180 million people are infected with HCV; the U.S. prevalence of HCV infection is 1.6%, which equates to an estimated 4.1 million infected people.[2] However, more recent surveillance data suggest that HCV infection has increased to 5.2 million people in the U.S.[3] There are six genotypes of HCV, with a variety of subtypes of genotype 1 being the most prevalent in the Americas and Europe.

Transmission of HCV occurs via exposure to infectious blood. The population at highest risk for HCV transmission is intravenous drug users. Other risk factors are receipt of blood products and/or organ transplants prior to the blood screening initiative in 1992, needlestick injuries, multiple sex partners, being born to an HCV-positive mother, body piercing or tattoos, and hemodialysis. Higher rates of HCV infection are noted in incarcerated and homeless persons. The virus coats itself in low-density lipoproteins to enter the hepatocyte. Translation of ssRNA into a polyprotein occurs in the hepatocyte. Various enzymes cleave the viral polyprotein to allow assembly of a replication complex and viral replication occurs. The life cycle of the virus takes place entirely in the hepatocyte and does not involve integration into the host genome; this is why HCV infection can be eradicated, unlike other chronic viral infections.

Of those with acute HCV infection, 20% will have spontaneous resolution and clear the virus without medication. The remaining 80% will continue to have chronic HCV infection, which is a slow, progressive disease. The liver damage is associated with cell-mediated inflammation, and rapid cell destruction and turnover may cause hepatocellular carcinoma to develop. Thirty percent of chronic HCV infections will result in cirrhosis of the liver, and 25% of cirrhotic persons will ultimately die from liver failure or liver cancer unless they receive a liver transplant.

Since approval in 1991, interferon has become a backbone in the treatment of patients infected with HCV, providing a sustained virological response (SVR) in 15% to 25% of patients with genotype 1 infection when given as monotherapy.[4] The use of interferon alfa in combination with ribavirin almost doubled the response rates in genotype 1 infection, whereas genotype 2 or 3 patients had SVR rates of 70% to 85%.[5] For more than a decade, there were no other classes of medications to augment treatment of genotype 1, but in 2011, the NS3/4A protease inhibitors boceprevir (Victrelis, Merck) and telaprevir (Incivek, Vertex) became available for the treatment of patients with HCV genotype 1 infection.

A combination of a protease inhibitor with pegylated interferon alfa-2a (Pegasys, Roche) and ribavirin provided SVR rates of 68% to 75% in treatment-naïve patients with genotype 1.[6,7] However, the regimen had significant limitations due to contraindications and intolerance to interferon therapy, additive adverse effects of anemia from ribavirin, a low genetic barrier to the development of resistance inherent to protease inhibitors, and frequent dosing intervals.[8,9] Several potent direct-acting antiviral (DAA) agents are being investigated to address the need for interferon-free, all-oral therapies.

Sofosbuvir (Sovaldi, Gilead Sciences) is a nucleotide analogue NS5B polymerase inhibitor approved by the Food and Drug Administration on December 6, 2013, for the treatment of chronic HCV infection as a component of a combination antiviral treatment regimen.[10] This article reviews the pharmacology, pharmacodynamics, pharmacokinetics, resistance profile, clinical efficacy, safety data, and current role in therapy for this agent.

PHARMACOLOGY

Sofosbuvir, a phosphoramidate prodrug, is chemically described as (*S*)-Isopropyl 2-((S)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate.[10] Figure 1 shows the chemical structure of sofosbuvir. A uridine nucleotide analogue, it produces its antiviral effect by inhibiting NS5B RNA polymerase enzyme. The replication of HCV requires NS5B, an RNA-dependent RNA polymerase, which is responsible for the synthesis of both positive-strand genomic RNA and negative-strand RNA.[12] Sofosbuvir mimics the natural substrate of NS5B polymerase and becomes incorporated into the growing RNA, inducing a chain termination event.[13]

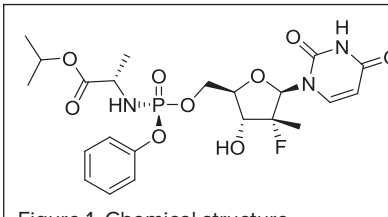

Figure 1 Chemical structure of sofosbuvir.[10]

PHARMACOKINETICS

Originally, GS-9851, a mixture of two diastereoisomers—sofosbuvir (GS-7977) and GS-491241—was discovered as an agent with high potency and selectivity for NS5B inhibition. Pharmacokinetic and pharmacodynamic parameters have been evaluated for GS-9851; however, after development of a method of separat-

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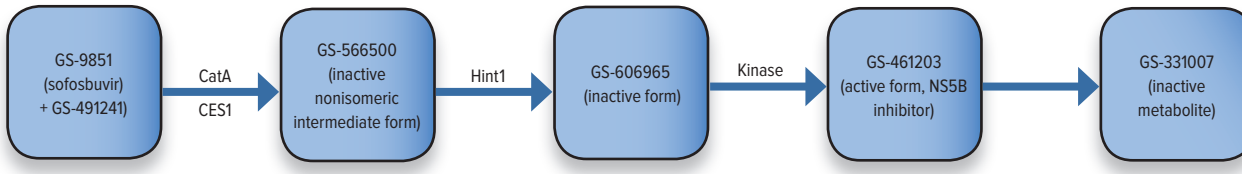

Figure 2 The proposed metabolic pathway of GS-9851.[14]

ing isomers, sofosbuvir was selected for further development as the more active inhibitor of the RNA polymerase. Since both isomers of GS-9851 share the same metabolic pathway,[14] the results can be applied to sofosbuvir.

An *in vitro* study suggests that GS-9851 is a prodrug that is converted into the inactive, nonisomeric intermediate form with the aid of two enzymes: cathepsin A (CatA) and carboxylesterase 1 (CES1). Further, histidine triad nucleotide-binding protein 1 (Hint1) hydrolyzes the compound into an inactive monophosphate form, which is then metabolized by kinase enzymes into the active form (GS-461203) that inhibits NS5B RNA polymerase.[14] As a result of this specific metabolism, sofosbuvir has a low potential for cytochrome P450–mediated drug–drug interactions. The proposed metabolic pathway of GS-9851 is depicted in Figure 2. A summary of the pharmacokinetics of sofosbuvir and subsequent metabolites is presented in Table 1.[15] Renal clearance is the main elimination pathway of sofosbuvir, which may pose a problem in those with renal impairment.

RESISTANCE PROFILE

NS5B RNA polymerase inhibitors can be divided into two groups: nucleos(t)ide analog inhibitors, including sofosbuvir, and non-nucleoside inhibitors. Nucleos(t)ide analogue NS5B polymerase inhibitors, as a class, have a high genetic barrier to resistance. They target the active center of NS5B, which is a highly conserved region of the viral genome, and a change in the amino acid sequence may result in either a loss of function of NS5B polymerase or a significant decrease in the replication fitness of the virus.[16] *In vitro* study has demonstrated that only the S282T amino acid change decreases the inhibitory activity of sofosbuvir.[17] Sofosbuvir, as one of the nucleos(t)ide analog inhibitors, has a distinct resistance profile that does not overlap with the non-nucleoside NS5B protease inhibitors, making sofosbuvir an attractive team player for potential treatment combinations.[18]

In vivo resistance data are very limited. Only one patient was found to have the S282T variant after the end of treatment for sofosbuvir, indicating resistance to sofosbuvir is extremely uncommon.[18] In addition, clinical trials[19,20] have demonstrated high rates of SVR in up to 90% of patients, and in the few patients with virological failures, resistant virus did not emerge, which confers a high genetic barrier to resistance of sofosbuvir.

PIVOTAL CLINICAL TRIALS

Treatment-Naïve Patients

The FISSION Trial[19]

Lawitz et al. conducted a randomized, open-label, active-control, phase 3 study to compare the efficacy and safety of sofosbuvir (SOF) plus ribavirin (RBV) versus peginterferon alfa-2a (PEG) plus RBV in patients with genotype 2 or 3 infection who had not previously received treatment for HCV infection.

A total of 499 patients (mean age, 48 years) with genotype 2 or 3 infection received either SOF 400 mg orally once daily plus RBV orally 1,000 mg/day or 1,200 mg/day in divided doses in patients with a body weight of less than 75 kg or at least 75 kg, respectively, for 12 weeks, or the previous standard of care, PEG 180 mcg subcutaneous injection (SC) once weekly plus RBV 800 mg orally daily in two divided doses for 24 weeks. Note the higher dose of RBV used in the SOF arm. The primary efficacy endpoint was a sustained virological response defined as an HCV RNA level below the lower limit of quantification at 12 weeks after the end of treatment (SVR12).

With respect to the primary endpoint, the FISSION study demonstrated noninferiority of the SOF+RBV regimen as compared with PEG+RBV. Both groups, SOF+RBV and PEG+RBV, demonstrated the same rate of SVR of 67%; however, the results differed greatly among genotypes. In the SOF+RBV group, SVR was observed in 97% of patients with genotype 2 infection and in only 56% of patients with genotype 3. The majority of patients enrolled in FISSION were infected with genotype 3 (more than 70%), which may explain why overall SVR rates in the SOF+RBV group were 67%. Thus, it is important to take into account that SOF+RBV has impressive SVR rates specifically in patients with genotype 2. Notably, only one patient on SOF+RBV had viral breakthrough with undetectable SOF plasma levels (presumably due to nonadherence), compared with 18 cases in the PEG+RBV group.

The authors concluded that the regimen of SOF+RBV was noninferior to PEG+RBV with a similar rate of SVR of 67% in previously untreated patients with genotype 2 or 3 infection. However, it is important to note that SOF+RBV response rates were much higher in patients with genotype 2 than patients with genotype 3 in the same treatment group.

The NEUTRINO Trial[19]

Lawitz et al. conducted another single-group, open-label, phase 3 study to evaluate efficacy and safety of SOF+RBV+PEG in previously untreated patients infected

Table 1 Pharmacokinetic Parameters of Sofosbuvir[15]

Parameter	Sofosbuvir
Absorption	Peak plasma concentration observed at 0.5–2 hours post-dose
Effect of food	None
Metabolism	Hydrolysis, phosphorylation, dephosphorylation
Elimination	Renal clearance (80% active metabolite recovered in urine)
Distribution	61–65% bound to human plasma proteins

with HCV genotype 1, 4, 5, or 6. Genotype1 accounts for the majority of HCV infections in the U.S. and has historically been harder to treat compared to genotype 2 or 3. Genotypes 4, 5, and 6 are not common in the U.S., and treatment advances have been largely deficient. Among the patients enrolled in the study, 89% had HCV genotype 1, 9% had genotype 4, and 2% had genotype 5 or 6, which is consistent with the U.S. prevalence of HCV genotypes.

A total of 327 patients received triple therapy with SOF 400 mg orally once daily plus RBV and PEG for a 12-week treatment duration. The primary efficacy endpoint was SVR12. The NEUTRINO study demonstrated a SVR rate of 90%. There were no major differences in SVR rates among groups with different genotype infection: 92% for patients with genotype 1a, 82% for genotype 1b, and 96% for genotype 4. All seven patients with genotype 5 and 6 had SVR in this trial. Patients without cirrhosis at baseline achieved SVR in 92% of cases, compared with 80% of patients who had cirrhosis at treatment initiation. The authors concluded that in treatment-naïve patients with HCV genotype 1 or 4 infection, the regimen of SOF+RBV+PEG for 12 weeks had high efficacy and noticeable reductions in adverse effects compared to the current standard of care.

Patients Without Treatment Options or Treatment-Experienced Patients

The POSITRON Trial[20]

POSITRON, a blinded, placebo-controlled study, was conducted to evaluate the efficacy and safety of SOF+RBV treatment in patients with HCV genotype 2 or 3 who had contraindications to interferon therapy, who had previously discontinued interferon therapy due to adverse events, or who had decided against interferon therapy for different reasons. Among the patients who were enrolled in the study, 51% had HCV genotype 2 infection and 49% had genotype 3.

A total of 278 patients with genotype 2 or 3 infection were randomized to receive either SOF 400 mg orally once daily plus RBV orally 1,000 mg/day or 1,200 mg/day divided into two doses in patients who weighed less than 75 kg or at least 75 kg, respectively (n = 207), or matching placebo (n = 71) for 12 weeks. The primary efficacy endpoint was SVR12.

The POSITRON study demonstrated a SVR rate of 78% in the SOF+RBV group compared with 0% of patients who received placebo ($P < 0.001$). None of the 153 evaluable patients had virological relapse after week 12. Similar to FISSION, in the treatment group SVR was observed in 93% of patients with HCV genotype 2 infection, compared with 61% of patients with genotype 3. The findings indicate that 12 weeks of treatment with SOF+RBV is an effective treatment option in patients with HCV genotype 2 or 3 infection for whom treatment with peginterferon is not an option.

The FUSION Trial[20]

FUSION, a blinded, active-control study, was conducted to evaluate the efficacy and safety of SOF+RBV in patients with HCV genotype 2 or 3 infection for whom prior treatment had failed: They did not respond to an interferon-containing regimen (25% of enrolled patients) or they had a relapse (75%).

To determine whether a longer treatment duration would have an effect on SVR, 201 patients received either SOF+RBV for 12 weeks followed by four weeks of placebo or a full 16 weeks of SOF+RBV. Among the patients who were enrolled in the study, 34% had HCV genotype 2 infection and 63% had genotype 3 (six patients were found to have genotype 1 after randomization and were excluded from the efficacy analysis).

Patients achieved SVR in 50% of cases in the 12-week group, compared to 73% in the 16-week group (difference, –23%, $P < 0.001$). The rates of SVR in patients without cirrhosis were significantly higher than those in patients with cirrhosis, as expected. However, in genotype 2 patients there was no difference between 12 versus 16 weeks of treatment, while in genotype 3 patients there was a significantly higher SVR rate when treated for 16 weeks. A relapse rate of 46% was observed among patients in the 12-week group, compared with 27% in the 16-week group. The authors concluded that 12 or 16 weeks of treatment with the SOF+RBV regimen was effective. The treatments had higher efficacy in patients with HCV genotype 2 infections and those without cirrhosis. By extending the SOF+RBV treatment duration even further, to 24 weeks of treatment in HCV genotype 3, SVR rates were increased to a comparable 84%, as seen in the VALENCE study.[21]

A summary of efficacy and safety results from these four pivotal clinical trials appears in Table 2.

ADVERSE EFFECTS

Sofosbuvir appears to be well tolerated compared to the traditional standard of care treatment options available, as evident in these phase 3 clinical trials.[19,20] No serious SOF-related adverse events were reported. Few moderate or severe adverse effects, grade 3 or 4 laboratory abnormalities, or treatment discontinuations were associated with SOF administration. Furthermore, investigators reported much lower rates of adverse events that can be attributed to SOF administration compared to PEG or RBV.

Because SOF was always used in combination with other antivirals, the adverse effects of SOF alone are difficult to determine. Nonetheless, the frequency of drug-related adverse events was lower in the SOF+RBV group compared with patients who received the PEG+RBV regimen in FISSION. Almost all common adverse events were at least 10% lower in the SOF+RBV group with the exception of anemia, which may be attributable to RBV. The most apparent difference was observed in influenza-like symptoms and depression, which was not surprising since they are limiting adverse effects of PEG.

In NEUTRINO, the most common adverse effects reported were fatigue, headache, nausea, insomnia, and anemia, all of which are consistent and comparable with PEG+RBV therapy from other clinical trials, suggesting that SOF does not worsen these adverse effects. In fact, adverse events led to treatment discontinuation in only 2% of patients. In both POSITRON and FUSION, the most common observed adverse events in the treatment groups were fatigue, nausea, headache, and insomnia. Although up to 13% of these patients had anemia, one cannot determine if it can be attributed to SOF, considering that RBV is known to cause hemolytic anemia. Refer to Table 3 for additional safety details.

SPECIAL POPULATIONS

HIV/HCV Co-Infection

Sofosbuvir and ribavirin for 12 or 24 weeks have been studied in HIV/HCV co-infected patients with genotypes 1, 2, or 3.[23] Although the SVR rates of genotype 2 and 3 were an impressive 88% and 92%, the

Table 2 Summary of Pivotal Clinical Trials[19,20]

Parameter		FISSION		NEUTRINO	POSITRON		FUSION	
Study		Randomized, open-label, active-control		Single-group, open-label	Blinded, placebo-controlled		Blinded, active-control	
Number		499		327	278		201	
Population		Previously untreated patients			Patients with HCV genotype 2 or 3 without treatment options			
		HCV genotype 2 or 3		HCV genotype 1, 4, 5, or 6	Peginterferon is not an option		Had no response to prior interferon-containing treatment	
Treatment group		SOF+RBV for 12 weeks (n = 256)	PEG+RBV for 24 weeks (n = 243)	SOF+RBV+PEG for 12 weeks (N = 327)	SOF+RBV for 12 weeks (n = 207)	Placebo for 12 weeks (n = 71)	SOF+RBV for 12 weeks (n = 100)	SOF+RBV for 16 weeks (n = 95)
SVR, %		67	67	90	78	0	50	73
SVR by genotype, %	1			89.4				
	2	97.1	77.6		92.7	0	86.1	93.8
	3	55.7	62.5		61.2	0	29.7	61.9
	4, 5, 6			97.1				
SVR by cirrhosis, %	No	72.1	74.1	92.3	80.7	0	60.9	76.2
	Yes	46.9	38.0	79.6	61.3	0	30.6	65.6
Virologic breakthrough		1	18	0	0	—	0	0
Relapse in completers, %		29	20	8	20	—	46	27
Anemia, %		7.8	11.5	20.8	13.0	0	10.7	4.1
Neutropenia, %		0	12.3	16.5	0	0	0	0
Depression, %		5.5	14.0	9.5	7.2	1.4	5.8	6.1
Influenza-like illness, %		2.7	18.1	15.6	3.9	2.8	1.0	3.1
Fatigue, %		36	55	59	44	24	45	47
Insomnia, %		12	29	25	19	4	20	29

HCV = hepatitis C virus; PEG = peginterferon; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response

SVR rate of genotype 1 was 76% without the presence of a third antiviral. The safety profile was analogous to the mono-infected patients in the phase 3 studies cited earlier. Because of these results from the PHOTON-1 study, sofosbuvir is the first DAA to have an FDA-approved indication for treatment in HIV/HCV co-infection.[10]

Hepatocellular Carcinoma Awaiting Liver Transplant

Patients with hepatocellular carcinoma (HCC) regardless of genotype who met the MILAN criteria (defined as the presence of a tumor no more than 5 cm in diameter and no more than three tumors that are each 3 cm or less in diameter) were given SOF+RBV for 24 to 48 weeks, or until liver transplant.[24] Of the patients whose HCC was undetectable at the time of transplant, 64% (23 of 36) maintained post-transplant virological suppression. The safety profile of SOF+RBV was comparable to mono-infected patients in phase 3 trials. Subsequently, sofosbuvir became the first DAA to have an FDA-approved indication for treatment of HCC patients awaiting liver transplantation for up to 48 weeks or until liver transplant.[10]

Renal Impairment

There are no dose recommendations for sofosbuvir in patients with an estimated creatinine clearance below 30 mL/min or end-stage renal disease requiring hemodialysis. Safety and efficacy have not been established, and until the results of ongoing studies are available, sofosbuvir should not be recommended in patients with several renal impairment.

Combinations With Other New Direct-Acting Antiviral Agents

A summary of interferon-free treatment options is presented in Table 4.

The COSMOS Trial[25,26]

COSMOS, a randomized, open-label, phase 2a study, was conducted to evaluate the efficacy and safety of 12 or 24 weeks of SOF plus simeprevir (Olysio, Janssen Pharmaceuticals). Simeprevir (SMV) is a NS3/4A protease inhibitor that the FDA approved in November 2013. SOF and SMV were administered with or without RBV in patients with HCV genotype 1 who were null responders to prior therapy with PEG. Patients were enrolled into two cohorts based on the degree of inflammation and fibrosis of the liver quantified by METAVIR score (F0–F2, and F3–F4).

Table 3 Safety Data From Four Phase 2 Studies (N = 778)[22]

Therapy	SOF 12 Weeks	SOF+RBV 8–12 Weeks	SOF+RBV 24 Weeks	SOF+PEG/RBV 8–12 Weeks	SOF+PEG/RBV 24 Weeks	SOF+LDV+RBV 24 Weeks
Number of patients	10	130	157	164	280	34
Grade ≥3 AE	0	2 (2%)	12 (8%)	27 (16%)	44 (16%)	3 (9%)
Grade ≥2 AE	4 (40%)	43 (33%)	67 (43%)	116 (71%)	199 (71%)	14 (41%)
Serious AE	0	4 (3%)	6 (4%)	6 (4%)	10 (4%)	2 (6%)
AE leading to discontinuation	0	1 (< 1%)	2 (< 1%)	7 (4%)	27 (10%)	2 (6%)
Anemia	0	2 (2%)	4 (3%)	16 (10%)	33 (12%)	2 (6%)
Neutropenia	0	0	0	21 (13%)	34 (12%)	0
Nausea	0	1 (< 1%)	5 (3%)	13 (8%)	18 (6%)	0
Diarrhea	0	1 (< 1%)	7 (4%)	2 (1%)	11 (4%)	0
Fatigue	1 (10%)	5 (4%)	17 (11%)	23 (14%)	35 (13%)	0
Headache	0	6 (5%)	9 (6%)	13 (8%)	29 (10%)	1 (3%)
Arthralgia	0	2 (2%)	1 (< 1%)	10 (6%)	14 (5%)	0
Anxiety	0	3 (2%)	8 (5%)	8 (5%)	15 (5%)	0
Insomnia	0	1 (< 1%)	10 (6%)	17 (10%)	23 (8%)	1 (3%)
Depression	0	1 (< 1%)	8 (5%)	9 (6%)	14 (5%)	2 (6%)
Dyspnea	0	0	8 (5%)	6 (4%)	12 (4%)	0

AE = adverse event; LDV = ledipasvir; PEG = peginterferon; RBV = ribavirin; SOF = sofosbuvir

The results for cohort 1 demonstrated SVR of 96% and 93% in the 12-week SOF+SMV+RBV and SOF+SMV arms, respectively. No viral breakthroughs during treatment were observed. Viral relapse after end of treatment occurred in two patients (both during the first four weeks of follow-up), one patient in each of the 12-week arms. No resistance to SOF and one case of emerged resistance to SMV were identified. The results for cohort 2 demonstrated undetectable viral loads at week 12 after treatment completion in 93% of the SOF+SMV+RBV arms and 93% to 100% of the SOF+SMV arms. Three viral relapses were observed by eight weeks after the end of treatment. No viral breakthroughs were reported.

The investigators concluded that SOF plus SMV with or without RBV for 12 weeks provided high SVR rates in prior null responders with HCV genotype 1. The most recent guidelines for the treatment of hepatitis C, written in February 2014, incorporated the encouraging results of the COSMOS study to justify the all-oral regimen as first-line treatment in patients who are ineligible for peginterferon or have had past treatment failures.[27]

The Sofosbuvir/Daclatasvir Trial[28]

A randomized, open-label, parallel-group, phase 2a study was conducted to evaluate the efficacy and safety of SOF plus daclatasvir (DCV, a NS5A inhibitor) with or without RBV for 24 weeks in patients with chronic HCV genotype 1 who failed prior treatment with telaprevir or boceprevir plus PEG+RBV.

In this study, 41 noncirrhotic patients with a METAVIR score of 2 or more, HCV genotype 1, and previous breakthrough, relapse, or nonresponse to the traditional standard of HCV treatment received SOF 400 mg orally daily plus DCV 60 mg orally daily either with or without RBV for 24 weeks. SVR12 was achieved in 95% (one patient was unavailable at post-treatment week 12 but had undetectable HCV at treatment week 24) and 100% of the patients treated with and without RBV, respectively. No breakthrough or relapses were observed. Both treatment regimens were very well tolerated.

The authors reported that the all-oral, once-daily combination of SOF plus DCV with or without RBV achieved SVR in all HCV genotype 1–infected patients who had failed the past gold standard triple therapy of an NS3/4A protease inhibitor, PEG, and RBV.

The ION Studies[29–31]

Results from three phase 3 studies announced in December 2013 evaluated the once-daily fixed-dose combination of sofosbuvir and a NS5A inhibitor, ledipasvir (LDV). ION-1 studied the fixed-dose combination SOF/LDV with or without RBV for 12 weeks in genotype 1 treatment-naïve patients. ION-2 studied SOF/LDV with or without RBV for 12 or 24 weeks in genotype 1 treatment-experienced patients. And ION-3 studied SOF/LDV with or without RBV for eight or 12 weeks in genotype 1 treatment-naïve noncirrhotic patients.

SVR rates of the 1,518 patients in all three trials were above 93%. The results were significant in demonstrating three major points: 1) The addition of RBV to SOF/LDV did not provide any clinical benefit; 2) SOF/LDV for 12 weeks resulted in high SVR rates, even in treatment-experienced patients; and 3) Genotype 1 treatment-naïve patients without cirrhosis may only need eight weeks of treatment.

Gilead Sciences (the developer of both drugs) submitted the fixed-dose combination of SOF/LDV to the FDA for approval in the first quarter of 2014. With approval, this would be the first single-tablet regi-

Table 4 Summary of Sofosbuvir and Direct-Acting Antiviral Trials (Genotype 1 Null Responders Only)[25,26,28–31]

Trial	ION Trials			COSMOS, Cohort 1 & 2				SOF+DCV Trial	
Treatment	ION-1 SOF/LDV ± RBV	ION-2 SOF/LDV ± RBV	ION-3 SOF/LDV ± RBV	Cohort 1 SOF+ SMV+ RBV	Cohort 1 SOF+ SMV	Cohort 2 SOF+ SMV+ RBV	Cohort 2 SOF+ SMV	SOF+ DCV	SOF+ DCV+ RBV
Number of patients	431	440	647	51	29	57	30	21	20
Treatment duration, weeks	12	12 or 24	8 or 12	12 or 24	12 or 24	12 or 24	12 or 24	24	24
SVR12	97%–98%	94%–99%	93%–95%	79%–96%	93%–94%	93%	93%–100%	100%	95%
Breakthrough	0	0	0	0	0	0	0	0	0
Relapse	—	—	1	1	1	2	1	0	0
Serious AE	0	0	0	0	0	3	1	0	1 (5%)
AE that led to discontinuation	0	0	0	1	1	0	1	0	0

AE = adverse event; DCV = daclatasvir; LDV = ledipasvir; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response

men available for treatment of HCV genotype 1, which is vastly different than past standards of care.

DRUG INTERACTIONS

Clinically significant drug–drug interactions are minimal with sofosbuvir.[10] SOF is a substrate of the P-glycoprotein (P-gp) transporter, and potent inducers may decrease SOF plasma concentrations, potentially leading to treatment failure. However, SOF itself does not have an effect on concentrations of P-gp substrates. Classes of medications that are potent P-gp inducers and should be avoided are: anticonvulsants, rifamycins, and tipranavir, as well as the herb St. John's wort. With the exception of tipranavir, drug interactions are not anticipated with HIV antiretrovirals, a great advantage for use in co-infected patients.

DOSAGE AND ADMINISTRATION

Sofosbuvir is a 400-mg tablet to be taken once daily with or without food for 12 weeks. It has been approved for treatment of HCV genotypes 1, 2, 3, or 4 as part of a combination regimen.[10]

Sofosbuvir was recently established as part of every preferred regimen in the 2014 recommendations for treating hepatitis C.[27] In genotype 1 treatment-naïve patients or relapsers who are PEG-eligible, the recommended regimen is SOF+PEG+RBV for 12 weeks. For patients considered PEG-ineligible, the recommended regimen is SOF+SMV±RBV for 12 weeks. In patients who have failed PEG+RBV in the past, the recommended regimen is SOF+SMV±RBV for 12 weeks.

HIV co-infected patients have the same recommended regimens with an additional option for PEG-ineligible treatment-naïve patients: SOF+RBV for 24 weeks. The recommended treatment regimen for genotype 2 patients is SOF+RBV for 12 weeks, regardless of treatment history. Treatment with SOF+RBV is also recommended for all genotype 3 patients, but for a longer duration of 24 weeks.

COST

The wholesale acquisition cost of a 28-day supply of sofosbuvir is $28,000. At $1,000 per pill, the cost has stirred warranted concerns about justifying a treatment course with SOF. Considering that the majority of HCV-infected patients have been waiting for all-oral, PEG-free regimens, third-party payers will receive an increasing number of requests for a SOF+SMV regimen rather than SOF+PEG+RBV. The costs and expected SVR rates of current and past treatments are presented in Table 5.

P&T COMMITTEE CONSIDERATIONS

Sofosbuvir is a first-in-class nucleotide NS5B inhibitor. The efficacy of SOF in achieving SVR has been demonstrated in several phase 2 and 3 clinical trials; however, HCV genotype must be taken into account.

In treatment-naïve patients with genotype 1 and 4 infections, NEUTRINO showed a 90% SVR rate. With the use of SOF, the treatment duration of triple therapy (SOF+PEG+RBV) can be decreased to 12 weeks with many fewer adverse effects compared to the past standard of care using PEG, RBV, and either telaprevir or boceprevir. In addition, for PEG-ineligible patients or those for whom PEG+RBV treatment failed, treatment with SOF and simeprevir can result in SVR rates of 93% to 100%.

In genotype 2 treatment-naive patients, SOF provides superior SVR rates compared with the past standard of care using peginterferon and ribavirin. FISSION demonstrated a 97% SVR rate in patients with genotype 2 infection who received SOF and RBV for 12 weeks, compared with 78% receiving PEG and RBV for 24 weeks. In treatment-experienced patients (prior null responders) or in those who could not use PEG, both FUSION and POSITRON demonstrated high SVR rates ranging from 86% to 93%.

Genotype 3 patients do not have the same robust response to SOF and require an extended treatment duration of 24 weeks. In the pivotal clinical trials, treatment-naive patients had SVR rates ranging from 56% to 62%. But when treatment duration was extended in subsequent studies, SOF and RBV for 24 weeks demonstrated improved SVR rates of 84%.

Sofosbuvir is associated with the following advantages:

- It is highly effective in genotype 2 patients.

Table 5 Costs of Current Therapies for Hepatitis C Infection[32,33]

Drug*	Dose	12 Weeks	24 Weeks	44 Weeks	48 Weeks
Peginterferon alfa-2a	180 mcg subcutaneously once weekly	$6,000	$12,000	—	$24,000
Ribavirin	1,200 mg daily	$3,000	$6,000	—	$12,000
Telaprevir	1,125 mg twice daily	$66,155	—	—	—
Boceprevir	800 mg three times daily	—	$40,120	$73,554	—
Simeprevir	150 mg once daily	$66,360	—	—	—
Sofosbuvir	400 mg once daily	$84,000	$168,000	—	—

Complete Treatment Regimen	Cost of Treatment Course	SVR Rate
Sofosbuvir + peginterferon + ribavirin, 12 weeks	$93,000	90%
Sofosbuvir + simeprevir, 12 weeks	$150,360	> 93%
Sofosbuvir + ribavirin, 24 weeks	$174,000	76% (genotype 1) 84% (genotype 3)
Sofosbuvir + ribavirin, 12 weeks	$87,000	> 92%
Living with compensated cirrhosis	$270,000	--
Liver transplantation	$577,100	--

* Drug costs are based on wholesale acquisition cost.

- It provides a shorter treatment duration for genotype 1 patients.
- It is easy to take (one pill once daily).
- It has a favorable adverse-effect profile.
- There is a high barrier to resistance.
- It has been studied in combination with other DAAs for interferon-free treatment regimens.
- It is part of all first-line HCV treatment recommendations in the 2014 guidelines of the Infectious Diseases Society of America and American Association for the Study of Liver Diseases.

The disadvantages are a lack of improvement in SVR rates for genotype 3 patients and a high cost of treatment. Although the price is significantly higher than other treatment options, one must consider the cost per SVR rather than just the acquisition cost of medications. A patient who fails substandard treatment will eventually either have to be treated again with expensive antivirals or suffer the cost of living with decompensated cirrhosis or liver transplantation, all of which far outweigh the current cost of treatment with the new oral DAAs.

CONCLUSION

Sofosbuvir, a novel antiviral effective against multiple HCV genotypes, has the potential to play an essential role in the care of both treatment-naïve and treatment-experienced patients. SOF regimens offer an interferon-free option in genotypes 2 and 3 infections. In genotype 1 and 4 infections, the use of SOF can decrease the pill burden, length of treatment, and adverse-effect profile compared to the past standard of care. SOF can be used in combination with other DAAs to provide an interferon-free option for genotype 1 infections as well, according to the 2014 recommendations for hepatitis C treatment. Sofosbuvir is the first DAA to be FDA-approved for HIV co-infected patients and those awaiting liver transplantation.

Several trials are evaluating the use of SOF with other oral DAAs that will provide additional all-oral interferon-free treatment regimens for genotype 1 infections. Moreover, SOF is expected to be available as a fixed-dose combination with ledipasvir by the end of 2014. The paradigm of chronic HCV treatment is changing rapidly, and sofosbuvir will play an important role in the near future.

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